Deproteinized bovine bone mineral is non-inferior to deproteinized bovine bone mineral with 10% collagen in maintaining the soft tissue contour post-extraction: A randomised trial

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Abstract: OBJECTIVES To test the non-inferiority of demineralized bovine bone mineral (DBBM) compared to demineralized bovine bone mineral with 10% collagen (DBBM-C) for the maintenance of the soft tissue contour after tooth extraction in the esthetic zone. MATERIAL AND METHODS Sixty-five patients randomly received ridge preservation at a single site in the anterior maxilla with DBBM or DBBM-C. Both, DBBM and DBBM-C were covered with a collagen matrix. Profilometric analyses were performed at baseline (BL), immediately after treatment (PO) and at 4 months (FU; day of implant placement). The main outcome was the horizontal mean change (HC) at the buccal aspect. The measurements also included changes of the estimated soft tissue thickness (eTT) at 1mm, 3mm and 5mm below the buccal gingival margin. Descriptive analysis was performed and differences between groups were analyzed using independent samples t-test. The non-inferiority test was performed for HC. RESULTS At 4 months, the horizontal mean change (HC) was -1.43mm (±0.53mm) (DBBM-C) and -1.32mm (±0.53mm) (DBBM). Change of the estimated soft tissue thickness (eTT) between baseline (BL) and four months of follow-up (FU) at 1mm, 3mm and 5mm amounted to -4.58mm (±2.02mm), -2.40mm (±0.97mm) and -1.37mm (±0.78mm) for DBBM-C and to -4.12mm (±1.80mm), -2.09mm (±0.91mm) and -1.23mm (±0.72mm) for DBBM. The differences between the groups were not statistically significantly for any of the outcome measures ($p > .05$). CONCLUSIONS DBBM is non-inferior to DBBM-C for the maintenance of the soft tissue contour 4 months after tooth extraction.

DOI: https://doi.org/10.1111/clr.13570

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Article type : Original Research

Deproteinized bovine bone mineral is non-inferior to deproteinized bovine bone mineral with 10% collagen in maintaining the soft tissue contour post-extraction: A randomised trial

Running title: Soft tissue contour post-extraction

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Acknowledgments: This study was supported by a research grant from Geistlich Pharma AG, Wolhusen, Switzerland.
Conflict of Interest: The authors report no conflict of interest.

V.MS., A.H.L., J.B.C.N., R.E.J., D.S.T., C.H.F.H and G.A.R. conceived the ideas; V.M.S. and A.H.L collected the data; V.M.S., C.M.P. and J.B.C.N. analyzed the data; and V.M.S., J.B.C.N., R.E.J., D.S.T., C.H.F.H and G.A.R. led the writing.

Abstract

Objectives: To test the non-inferiority of demineralized bovine bone mineral (DBBM) compared to demineralized bovine bone mineral with 10% collagen (DBBM-C) for the maintenance of the soft tissue contour after tooth extraction in the esthetic zone. **Material and Methods:** Sixty-five patients randomly received ridge preservation at a single site in the anterior maxilla with DBBM or DBBM-C. Both, DBBM and DBBM-C were covered with a collagen matrix. Profilometric analyses were performed at baseline (BL), immediately after treatment (PO) and at 4 months (FU; day of implant placement). The main outcome was the horizontal mean change (HC) at the buccal aspect. The measurements also included changes of the estimated soft tissue thickness (eTT) at 1mm, 3mm and 5mm below the buccal gingival margin. Descriptive analysis was performed and differences between groups were analyzed using independent samples t-test. The non-inferiority test was performed for HC. **Results:** At 4 months, the horizontal mean change (HC) was -1.43mm (±0.53mm) (DBBM-C) and -1.32mm (±0.53mm) (DBBM). Change of the estimated soft tissue thickness (eTT) between baseline (BL) and four months of follow-up (FU) at 1mm, 3mm and 5mm amounted to -4.58mm (±2.02mm), -2.40mm (±0.97mm) and -1.37mm (±0.78mm) for DBBM-C and to -4.12mm (±1.80mm), -2.09mm (±0.91mm) and -1.23mm (±0.72mm) for DBBM. The differences between the groups were not statistically significantly for any of the outcome measures ($p>0.05$). **Conclusions:** DBBM is non-inferior to DBBM-C for the maintenance of the soft tissue contour 4 months after tooth extraction.

Key words: soft tissue; bone substitutes; profilometric analysis; ridge preservation.
Brazilian Clinical Trials Registry (ReBec: RBR-354q7d)

Introduction

The natural repair response of an intact socket after tooth extraction is composed of bone resorption and neoformation (Devlin & Ferguson 1991). In order to increase the predictability of implant therapy and esthetic outcomes, different techniques using a variety of materials were used to limit alveolar ridge resorption following tooth extraction (Barone et al. 2008; Araújo & Lindhe 2009; Jung et al. 2013; Araújo et al. 2015a; Meloni et al. 2015; Scheyer et al. 2016; Natto et al. 2017; Nart et al. 2017). A recent systematic review (Avila-Ortiz et al. 2019) evaluating radiographic outcomes found a significant reduction of the vertical ridge resorption, whilst the horizontal resorption was inconsistent. However, there is lack of evidence that directly correlates radiographic findings with the soft tissue contour after healing.

Despite the large number of studies investigating the impact of alveolar ridge preservation techniques (ARP) on radiographic parameters, few studies investigated its consequences on changes of the soft tissue contour (Fickl et al. 2009; Clozza et al. 2012; Schneider et al. 2014; Barone et al. 2016; Sbordone et al. 2017; Tomasi et al. 2018) Recent studies combined data from maxillary and mandibular sites, and also included premolars. In addition, the sample size was mostly limited and underpowered. Based on these clinical and pre-clinical trials, aiming to evaluate soft tissue remodeling with the use of optically scanned cast models, the radiographic bone loss is consistent with changes of the soft tissue contour (Fickl et al. 2009; Thalmair et al. 2013; Schneider et al. 2014). It has been suggested that soft tissues change seem to compensate for bone remodeling, thereby reducing the overall loss of the alveolar ridge contour (Benic et al. 2012; Kuchler et al. 2016). However, additional studies with a suitable design and inclusion criteria are necessary to confirm or

refute this hypothesis and could also contribute to clarify possible influences of different materials on the magnitude of such effect. Moreover, few studies compared the effect in the soft tissue contour (Schneider et al. 2014) in terms of cost-benefit, being DBBM-C more costly compared to DBBM alone. Another relevant aspect is that a considerable number of studies use DBBM-C instead of DBBM for ARP (Araujo & Lindhe 2005; Jung et al. 2013; Meloni et al. 2015; Araújo et al. 2015b) and many practitioners prefer handling DBBM-C.

Thus, the objective of the present RCT was to test non-inferiority of demineralized bovine bone mineral (DBBM) compared to demineralized bovine bone mineral with 10% collagen (DBBM-C) in the maintenance of the soft tissue contour after tooth extraction in the esthetic zone.

Material and Methods

Study design

This study reports the profilometric data of a randomized, controlled, double-blind, parallel non-inferiority clinical trial (Llanos et al. 2019).The primary outcome was the horizontal ridge width 1 mm below the buccal alveolar crest changing, evaluated 4 months post-extraction using CBCTs. The patients were treated at the Dental Clinic of Periodontology, University of São Paulo, São Paulo, Brazil. The study was approved by the Ethical Review Board (Dental School, n° 1.664.774), registered at the Brazilian Clinical Trials Registry (ReBec: RBR-354q7d) and conducted in accordance with the Helsinki Declaration of 1975 as revised in 2003. Enrolled patients signed an informed consent prior to the start of the study. The present study is in compliance with CONSORT.

Patients scheduled for single-tooth extractions in the maxilla (canines, lateral and central incisors) due to caries, endodontic complications, orthodontic and prosthetic reasons were screened. Subjects that fulfilled the following inclusion criteria's were included: age >18 years, need of tooth extraction of maxillary canines, lateral and central incisors, undergone anterior ridge preservation with defects ≤50% of the total height of the buccal plate, presence of one adjacent tooth at the extraction site, bleeding on probing and plaque index <20%, systemically healthy with no contraindication for oral surgical procedures and signed Informed Consent Form. Patients pregnant or lactating, with presence of bone metabolic disease, presenting defects >50% of the total height of buccal plate after tooth extraction, with severe periodontal disease or presence of acute periapical lesion on the target site and smokers (>10 cigarettes/day) were not included in the present study.

Procedures and Interventions

Two investigators screened the participants (A.H.L & V.M.S.).

Prior to extraction, the gingival phenotype (De Rouck et al. 2009) and the width of keratinized tissue were recorded at the center of the buccal aspect of the experimental site.

Only one surgeon (A.H.L) performed all tooth extractions and ridge preservation procedures. Flapless tooth extractions were performed, and the alveolus rinsed with saline solution after curettage and de-epithelialization of the sulcus. The integrity of the buccal bone wall and socket depth was checked with a periodontal probe immediately after extraction. The proportion of remaining buccal wall in relation to socket depth was calculated to determine whether the site fulfilled the local inclusion criteria. Patients presenting more than 50% of buccal bone loss were excluded from the study. Then, the patients were assigned to DBBM-C or DBBM group. The grafting materials were gently placed and adapted to the experimental site within the bony envelope at the level or slightly higher than the highest palatal bone plate. The CM was placed on top of the biomaterial and adapted to the soft tissue margins by six single interrupted sutures. All patients received a removable provisional and it was adjusted to avoid any contact to the surgical area.

Patients were randomly assigned to one of the two groups:

1. DBBM-C group: demineralized bovine bone mineral with 10% collagen (DBBM-C; Bio-Oss® Collagen, Geistlich Pharma AG, Wolhusen, Switzerland) + collagen matrix (CM; Mucograft Seal® Geistlich Pharma AG, Wolhusen, Switzerland) (n=33);
2. DBBM group: demineralized bovine bone mineral (DBBM; Bio-Oss®, Geistlich Pharma AG, Wolhusen, Switzerland) + CM (n=33).

Outcomes

Silicone impressions (Variotime, Heraeus Kulzer GmbH, Germany) were taken at baseline (BL: before tooth extraction; PO: immediately after final suture) and at 4 months (FU: 4 months follow-up). The impressions were used to obtain dental stone casts (GC Fujirock EP, GC Europe, Leuven, Belgium). Obtained casts were checked to assure perfect reproduction of the impressions. The casts were then optically scanned with a desktop 3D scanner (Imetric 3D, Courgenay, Switzerland). Afterwards, the acquired stereolithography (STL) files were uploaded to an image analysis software (Swissmeda Software; Swissmeda AG, Zurich, Switzerland) and automatically superimposed by the program (Fig. 1). A blinded,

calibrated (ICC> 0.97), examiner (V.M.S.) was the only responsible for the fine alignment of superimpositions and measurements of the following parameters:

1. Profilometric Measurements: the baseline casts (BL) were used to define the region of interest (ROI). The ROI was an area delimited at the buccal aspect of the experimental site by the following references: initially, the coronal border of the ROI followed the gingival margin at a distance of 1mm; vertical mesial and distal lines were drawn up to the mucogingival line (extended 3–6 mm apically); the mesial and distal reference lines were connected apically (Fig. 2a-d). The software calculated the Horizontal Changes (HC) within the selected ROI representing the mean horizontal change within that particular area, expressed in millimeters.
2. Linear measurements: the measurements were taken using the superimposed STL files using of a cross section through the center of each site (soft tissue contour changes between two time-points). A perpendicular line to the tooth axis was drawn. Four perpendicular lines to the tooth's axis were drawn up to the gingival margin (0, 1, 3 and 5 mm) to evaluate the estimated soft tissue thickness (eTT) (Fig. 3). The difference between the soft tissue outlines (BL, PO and FU) was assessed.

Sample size calculation

The sample size calculation was performed for the primary outcome of a previous study (ReBec: RBR-354q7d) i.e. change of the horizontal ridge width 1 mm below the buccal alveolar crest, evaluated 4 months post-extraction, with CBCT, which resulted in 33 patients per group. For the present study, a post-hoc profilometric sample size calculation was performed, considering a standard deviation of 0.5 mm and a noninferiority limit of 0.5mm at the area bordered by the mucosal margin (Schneider et al. 2014), a significance level of 5% and 95% statistical power. Based on this calculation, 44 patients would be necessary, 22 per group. Sixty-six patients were included to compensate for possible drop-outs. Each patient had one single experimental site. The present study revealed a power higher than 91% calculated after study conduction, considering HC as main outcome.

Randomization

A software was used to generate a random sequence (Random Allocation 2.0 Informer Technologies Inc.). Block sizes of n= 2 and n = 4 were used. Sequentially numbered opaque sealed envelopes were used for the allocation concealment.

Statistical analysis

The main outcome of this paper was the horizontal mean changes between the surfaces in mm (HC), 4 months after surgery. Intraclass Correlation Coefficient (ICC) was used to check the reproducibility of measurements in two datasets performed in different time points by the examiner (V.M.S.).

Descriptive analysis was performed and means and standard deviations for each group were recorded. The significant differences between groups were calculated using independent samples t-test. Confidence intervals of 95% (CI) were calculated. The non-inferiority test was performed for the HC only. To claim the non-inferiority of DBBM, the confidence interval was set within the range of -0.5mm to 0.5mm. For the secondary outcomes, superiority of DBBM-C over DBBM was tested using independent samples t-test. The level of significance was set at 5%.

Results

A total of 275 patients were initially screened, 82 patients received tooth extraction and 66 patients were included in the study and randomized for the treatments. Sixteen patients were excluded right after tooth extraction due to the presence of defects >50% of the total height of the buccal plate. One patient, assigned to the DBBM-C group, was lost during the follow-up period of 4 months. Sixty-five patients completed the follow-up period between March 2016 and June 2017 (Llanos et al. 2019). No major complications were

recorded. All patients presented both adjacent teeth to the analyzed area. The baseline demographic data for each group is presented in Table 1.

The main outcome (HC) was tested for non-inferiority between DBBM-C (reference) and DBBM (test treatment) (Fig. 4). Four months after ridge preservation, HC loss for the DBBM-C group presented -1.43mm (±0.53mm) whereas the DBBM group showed a loss of -1.32mm (±0.53mm) with a 95% confidence interval of 0.11 [-0.15; 0.37] and *p=0.62* (Table 2). Therefore, the DBBM group was non-inferior to the DBBM-C group. The obtained HC values were categorized in groups demonstrating changes of <1mm, 1-2mm and >2mm. Sixteen patients had <1mm of HC (5 DBBM-C and 11 DBBM), 42 had 1-2mm of HC (24 DBBM-C and 18 DBBM) and 7 had >3mm of HC (3 DBBM-C and 4 DBBM). Ten patients presented a thin phenotype, whereas 3 patients (1 DBBM-C and 2 DBBM) had <1mm of HC and 7 (2 DBBM-C and 5 DBBM) had 1-2mm of HC, no patients with a thin biotype showed >2mm of HC. No differences were found regarding the influence of gingival phenotype and the width of keratinized tissue among both groups ($p>0.05$). A correlation analysis between buccal bone thickness and soft tissue changes was performed with no significant correlation detected ($r = 0.18$, $p>0.05$).

The estimated soft tissue thickness (eTT) changes between BL and FU at 1mm, 3mm and 5mm below the buccal gingival margin were: -4.58mm (±2.02mm), -2.40mm (±0.97mm) and -1.37mm (±0.78mm) for DBBM-C and -4.12mm (±1.80mm), -2.09mm (±0.91mm) and -1.23mm (±0.72mm) for DBBM ($p>0.05$) (Table 3). The eTT between BL and PO at 1mm, 3mm and 5mm are listed in Table 4**.**

Discussion

The present study compared the profilometric changes after ridge preservation using two different biomaterials, DBBM versus DBBM-C, both in conjunction with a collagen matrix to seal the socket entrance. After 4 months, the use of DBBM was non-inferior to DBBM-C in terms of soft tissue contour changes in the anterior region of the maxilla (0.11mm; CI 95% -0.15 to 0.52). The horizontal mean changes (HC) between the surfaces were -1.43 mm of DBBC-C against -1.32 mm of DBBM. No significant differences between the groups were found for any of the parameters analyzed ($p>0.05$). The results of the present study are in line with previously published data, demonstrating changes of the soft tissue contour along with changes of the hard tissues following tooth extraction (Araujo & Lindhe 2005; Clozza et al. 2012; Jung et al. 2013; Schneider et al. 2014; Araújo et al. 2015b; Barone et al. 2016; Sbordone et al. 2017). However, methodological differences hamper a direct comparison of the studies.

The only study that allows for a direct comparison is Schneider *et al.* (2014), since they used the same methodology for profilometric analysis, a similar inclusion criteria of buccal bone loss and also included one group employing the same technique and biomaterials used as in the present investigation i.e. DBBM-C associated with CM for ARP. The horizontal mean changes for DBBM-C at HW-1 was slightly smaller when compared to the one showed in the present study (1.15mm ±0.5mm versus -1.43mm±0.53mm, respectively). Despite of all similarities, some details in the inclusion criteria and follow-up period may elucidate the numerical differences between these two studies. The follow-up of

the present study was 4 months, while Schneider *et al.,* (2014) had a longer healing period, i.e. 6 months. Also, the present study included 33 patients per groups and included exclusively maxillary anterior teeth. In contrast, Schneider *et al.* (2014) included 10 subjects in the group with DBBM-C and the experimental sites included premolars and/or lower teeth. According to previous studies, maxillary anterior teeth usually presents a thinner buccal bone wall when compared to premolars (Vera et al. 2012) and there is a negative correlation between buccal bone thickness and ridge resorption (Ferrus et al. 2010; Spinato et al. 2014; Tonetti et al. 2019). Such a finding corroborates with ours and explains, at least partially, the higher horizontal change of the present study in comparison to Schneider *et al.,* (2014). This could also be related to the lack of correlation between buccal bone thickness and soft tissue changes, as few patients presented a buccal bone thicker than 0.5mm, which is considered thin when compared to other sites (Tomasi et al. 2010).

CBCT analysis from the patients of the present study (Llanos et al. 2019) also demonstrated a small horizontal bone loss at 1mm (−1.60 ± 0.82 for DBBM-C and −1.37 ± 0.84 for DBBM). In terms of absolute values, the CBCT bone loss was close to the profilometric soft tissue changes, but not directly proportional. Some slight numerical differences were also observed when comparing each bone substitute, with an advantage for DBBM, without statistical significance. Such difference may suggest that, despite an apparent similar behavior to the final soft tissue volume, the materials might differently affect the ratio soft to hard tissue within the complete remodeling. However, from a clinical point of view, the soft tissue difference around 0.1 mm between groups would not be clinically relevant for the final esthetical outcome. Furthermore, more studies evaluating simultaneously both tissues are needed to clarify such point.

There are few clinical studies in the literature investigating soft tissue contour changes after tooth extraction. The existing studies also included premolars and mandibular teeth (Thalmair et al. 2013; Schneider et al. 2014; Barone et al. 2016; Sbordone et al. 2017; Tomasi et al. 2018) whereas the present study evaluated exclusively anterior maxillary teeth (canines and incisors), focusing in the esthetic outcomes. The previous studies in dental

literature have also a limited sample size, not reaching more than 14 patients per group (Barone et al. 2016) and 40 patients per study (Schneider et al. 2014).

Regarding the profilometric outcomes presented in the literature, different methods and measurements were reported, rendering the comparison between studies challenging. Fickl and collaborators (2007) found an overall reduction between 1.12 mm and 1.45 mm in volume per area (volume difference per measured area) after 4 months. Using a different primary outcome (expressed in mm^3) and two bone substitutes with porcine origin, Barone *et al.* (2016) found a mean loss of 244 mm^3 (pre-hydrated collagenated cortico-cancellous porcine bone group) and 349 mm^3 (cortical porcine bone group) after only 3 months. Another RCT with a negative control group and a DBBM test group (Sbordone et al. 2017) presented similar findings when compared to a previous study (Barone et al. 2016), always demonstrating an overall reduction from the original volume (expressed in mm^3), with a reduction of 400 mm^3 at control group and 210 mm^3 at DBBM group after 5 months. A recent RCT evaluating soft tissue changes in posterior sites after 6 months (Tomasi et al. 2018) found interesting results, where the DBBM-C showed a soft tissue remodeling of 21.3%, a similar amount in the negative control group (20%). In the aforementioned studies, the sites presented thick buccal bone wall, commonly observed in posterior regions, what doesn't favor the identification of differences between treatments. It is well recognized that thick buccal bone represents a lower degree of bone remodeling after extraction (Tomasi et al. 2010). In the present study, buccal bone walls were mostly thin, which allows a proper investigation of ARP technique and materials, demonstrating no differences between the tested bone substitutes.

Therefore, the high value of eTT-1 for both groups (-4.58mm ±2.02mm for DBBM-C and -4.12mm ±1.80mm for DBBM) was caused by vertical changes, that were more pronounced for that particular region.

In the present sample, 10 out of 65 subjects were classified as thin phenotype, 3 in the DDBM-C and 7 in the DBBM group. A secondary analysis comparing thin versus thick phenotypes didn't detect differences between these sub-groups. According to a recent systematic review (Avila-Ortiz et al. 2019), there is no study that evaluated ridge

preservation in relation to a prior phenotype classification. Interestingly, our findings were in contrast to the results previously reported by other authors which stated that thin phenotype could favor greater soft tissue remodeling (Kinaia et al. 2017). Such a difference may be associated to the clinical methodology of thickness measurement or to the experimental design (i.e. immediate implant placement vs. ridge preservation). Further studies should approach this topic in order to confirm such findings or to suggest improvements in the methodology to evaluate gingival phenotype. In addition, the KT band was also measured at the midbuccal aspect before tooth extraction. Despite being reported for the first time, correlation tests did not show any influence of a KT band on the degree of soft tissue remodeling.

The main limitation of the present study is the lack of a negative control group, without ARP procedure. Besides, this is a short-term evaluation and a prospective long-term analysis is necessary. Patient-related outcome measures focusing on esthetic analyses could also help to understand whether the results obtained in this study match with patients' expectations. Additionally, it is important to emphasize that the majority of the cases (89.2%) presented less than 2mm of HC, and 24.6% less than 1mm. This outcome leads to another question, determining the threshold value of HC change to consider successful, acceptable or unacceptable.

Conclusion

The use of demineralized bovine bone mineral (DBBM) is non-inferior compared to demineralized bovine bone mineral with 10% collagen (DBBM-C) for the maintenance of soft tissue contour after tooth extraction in the esthetic area of the maxilla.

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Tables

Table 1. Demographic data

	DBBM-C	DBBM
Age (years) Mean ± SD	41.9 ± 11.9	43.3 ± 10.3
Thick Phenotype/Thin Phenotype	29/03	26/07
Width of Keratinized Tissue	6.62 ± 1.56	6.41 ± 1.29
Central Incisor/Lateral Incisor/Canine	16/13/03	20/10/03

Table 2. Horizontal Changes of ridge width between baseline, immediate post-operative and 4 months follow-up

	DBBM-C	DBBM		Mean *p-value*
	Mean±SD	Mean±SD	Difference [95% CI]	
HC (mm)				
BL-PO	0.07±0.19	0.04±0.21	-0.25 [-0.12 ; 0.07]	*0.67*
BL-FU	-1.43±0.53	-1.32±0.53	0.11 [-0.15 ; 0.37]	*0.62*

Table 3. Analysis of estimated soft tissue thickness changes between baseline and 4 months follow-up

	DBBM-C	DBBM		Mean *p-value*
	Mean±SD	Mean±SD	Difference [95% CI]	
mm				
eTT-1	-4.58±2.02	-4.12±1.80	0.47 [-0.49 ; 1.42]	*0.83*
eTT-3	-2.40±0.97	-2.09±0.91	0.31 [-0.16 ; 0.78]	*0.19*
eTT-5	-1.37±0.78	-1.23±0.72	0.45 [-0.23 ; 0.52]	*0.42*
%				
eTT-1	-51.21±22.79	-45.27±20.69		
eTT-3	-23.45±10.23	-19.36±7.76		
eTT-5	-12.36±6.87	-10.61±5.78		

Table 4. Analysis of estimated soft tissue thickness changes between baseline and immediate post-operative

	DBBM-C	DBBM		Mean *p-value*
	Mean±SD	Mean±SD	Difference [95% CI]	
mm				
eTT-1	-0.18±0.61	-0.01±0.66	0.17 [-0.15 ; 0.48]	*0.93*
eTT-3	0.29±0.33	0.29±0.41	0.00 [-0.18 ; 0.19]	*0.34*
eTT-5	0.37±0.34	0.38±0.41	0.2 [-0.17 ; 0.20]	*0.54*
%				
eTT-1	-1.91±7.07	-0.13±7.61		

eTT-3	2.80±3.13	2.74±3.90
eTT-5	3.34±2.97	3.47±3.70

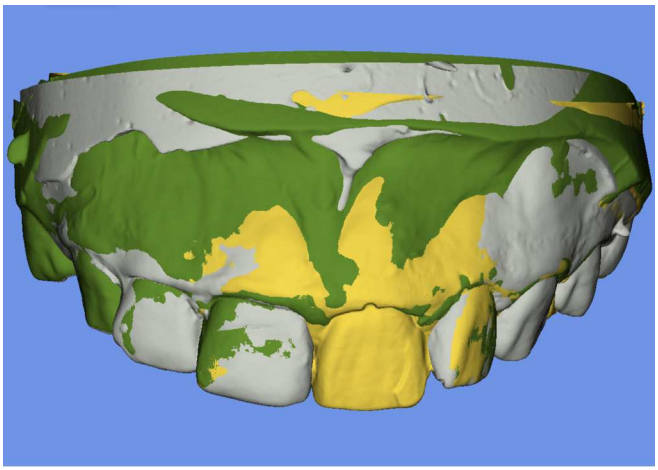
Figure Legends

Fig. 1. Stereolithography (STL) files superimposed. Baseline (BL: yellow), immediately after final suture (PO: green) and 4 months follow-up (FU: gray).

Fig. 2. Baseline cast (BL) with the region of interest (ROI) defined (a). Labial (b), lateral (c) and occlusal (d) views of analyzed area in orange (HC).

Fig. 3. A cross sectional view in the middle of the analyzed site showing the soft tissue outlines between timepoints. Outline of BL (yellow), PO (green) and FU (gray). eTT1, estimated tissue thickness at 1 mm below the gingival margin, eTT3, estimated tissue thickness at 3mm below the gingival margin, eTT5, tissue thickness at 5
mm below the gingival margin.

Fig. 4. Confidence Intervals and the Non-inferiority Margin of 0.5mm.



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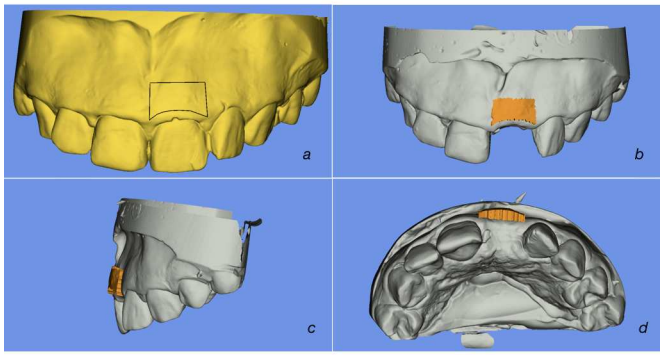

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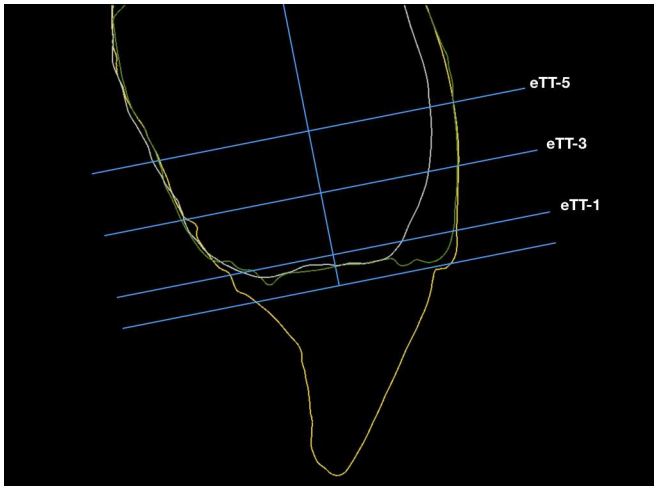

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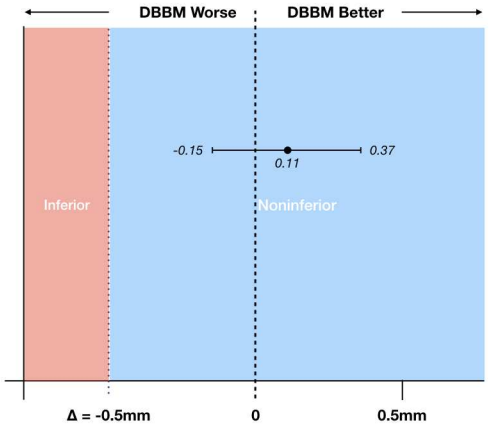

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